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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,943	07/25/2003	Joseph T. Rubino	AM-100802	3231

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EXAMINER	
POLANSKY, GREGG	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
06/21/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@howsonandhowson.com

Office Action Summary	Application No.	Applicant(s)	
	10/626,943	RUBINO ET AL.	
	Examiner	Art Unit	
	GREGG POLANSKY	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16,18 and 31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,18 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' response, filed 2/12/2010, to the Office action mailed 11/13/2009 is acknowledged. Applicants amended Claims 13 and 15, and presented arguments in response to the Office action.

2. Claims 13-16, 18, and 31-39 are pending and presently under consideration.

3. Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 13-16, 18, and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skotnicki et al. (U.S. Patent No. 5,362,718), in view of Waranis et al. (U.S. Patent No. 5516770) and Haeberlin et al. (UK Patent Application Publication GB 2327611). Maintained from previous Office action.

Skotnicki et al. teach hydroxyester derivatives of rapamycin, including the instantly claimed CCI-779 (rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid), and that these derivatives are useful as immunosuppressive, anti-inflammatory, antifungal, antiproliferative, and antitumor agents. See column 1, 1st paragraph and last paragraph, and column 12, "EXAMPLE 9". The reference suggests the rapamycin derivatives can be formulated with suitable carriers, including alcoholic solvents, and excipients for *inter alia* oral or parenteral administration. See columns 7 and 8.

Skotnicki et al. do not teach the formulations of CCI-779 recited by the instant claims.

Waranis et al. teach an injectable rapamycin solution comprised of a mixture of a concentrate of rapamycin in propylene glycol with a diluent of polyethylene glycol 400 and a polyoxyethylene sorbitan ester (e.g., polysorbate 80) and water (*see* Examples 1-3), yielding an injectable formulation concentration of rapamycin of 0.2 mg/ml to 4 mg/ml

(*see* column 2, lines 44-47), with 0.07-9.5% polysorbate 80 and 12-87% glycols (*see* column 3, lines 29-54). These concentrations are within the concentration ranges specified in the claims of the instant application.

Waranis et al. do not teach use of an antioxidant. Waranis et al. teach formulations of rapamycins, but not CCI-779 specifically. Waranis et al do not teach a formulation comprising ethanol (recited by instant Claims 32 and 38) or vitamin E (d,l-α-tocopherol) (recited by instant Claims 33, 34, 36, 38 and 39).

Haeberlin et al. teach the use of various carboxylic acids to stabilize (i.e., preserve) oral and parenteral formulations of macrolides, preferably a rapamycin. The reference teaches that macrolides [note: this would include CCI-779] are unstable upon storage, undergoing a variety of different degradation reactions and an acidic environment inhibits the degradation. See page 3. The preferred acids include malonic acid, oxalic acid, citric acid, and lactic acid (*see* page 4, lines 15-22). Haeberlin et al. teach a 0.05% to 5% acid concentration range and further disclose that the preferred amount of acid may be determined by routine experimentation. Haeberlin et al. give as an example, a formulation of a rapamycin with absolute (dehydrated) ethanol, Cremophor® EL (a surfactant), and citric acid. They present other examples of rapamycin formulations which include the use of 1,2 propylene glycol as a solvent and d,l-α-tocopherol (vitamin E) as an antioxidant. See pages 5-7.

It would have been obvious to one of ordinary skill in the art at the time of the invention, who was motivated to produce parenteral formulations of rapamycins, including CCI-779, to combine the teachings of Skotnicki et al., which discloses

hydroxyester rapamycin derivatives and formulations thereof, with those of Waranis et al. and Haeberlin et al., which teach rapamycin formulations. Waranis et al. teach the concentrations of the solvents (e.g., propylene glycol, absolute ethanol, and polyethylene glycol 400), rapamycin, and a specific surfactant (polysorbate 80) for a parenteral rapamycin formulation. Haeberlin et al. teach the instability of rapamycins and the need to use citric acid and d,l-α-tocopherol as a stabilizer in a rapamycin parenteral formulation. This would have motivated one to include citric acid/d,l-α-tocopherol in the formulations taught by the other two references. Since Skotnicki et al. do not teach specific formulations, one would have been motivated to find art teaching specific formulations of rapamycins, including CCI-779, such as is taught by Waranis et al. and Haeberlin et al. One would have been motivated to perfect a parental formulation of CCI-779 to reduce the bioavailability uncertainties of other forms of administration (e.g., oral), leading to more accurate and reproducible doses of the agent.

Response to Arguments

7. Applicants argue a *prima facie* case of obviousness based on overlapping ranges can be rebutted by showing the criticality of the claimed range. Applicants assert that they have presented a showing that the use of d,l-α-tocopherol outside of the claimed range "had negative effects including, without limitation, the generation of oxidative impurities." Applicants have presented U.S. Patent Application Pub. No. 2007/0142422 A1 (Rubino et al.) in support of this assertion (Example 3, at page 8).

The Examiner respectfully disagrees with Applicants' assertion of the criticality of the claimed concentration range of d,l-α-tocopherol and that the showing is counter to what is known and would be expected in the art, for the following reasons:

a. Example 3, at page 8 of Rubino et al. teaches "[s]amples of CCI-779 containing 0.2%, 0.5% and 1 % d,l-α-tocopherol" were used to study the effect of increase d,l-α-tocopherol concentration on the CCI-779 composition. Rubino et al. discloses that "for the samples containing 0.2% and 0.5% of α-tocopherol, the concentration of the oxidative impurities remained essentially unchanged, i.e., the concentration of oxidative impurities did not increase. However, there was an overall loss of potency of the samples due to the formation of other degradation products." Further, Example 3 of Rubino et al. discloses that "[f]or samples containing 1% α-tocopherol, the presence of the oxidative impurities drastically increased to 8.42%." However, Rubino et al. do not disclose any other constituents of the test compositions other than CCI-779 and d,l-α-tocopherol. Thus, it is not possible to make a comparison of the effects of d,l-α-tocopherol on the formation of oxidative impurities between the instantly claimed composition (Claim 31) and that which is disclosed in Example 3 of Rubino et al. Furthermore, Example 2 of Rubino et al. (page 8) presents data for three CCI-779 compositions, each comprising 2.5% CCI-779, 0.075% d,l-α-tocopherol, 0.0025% anhydrous citric acid, 39.5% dehydrate alcohol, and sufficient propylene glycol to bring the composition to the appropriate volume. The three compositions varied in the amount of oxidative/hydrolysis impurities initially

present (0.5%, 1% and 2%, respectively). The results of the study, after disclosed storage times, showed increased formation of oxidative/hydrolysis impurities which are correlated with the initial concentrations of oxidative/hydrolysis impurities (i.e., more oxidative/hydrolysis impurities were formed in the compositions as the initial oxidative/hydrolysis impurity concentrations increased). It is of important note that although 0.075% d,l-α-tocopherol (within the instantly claimed range for d,l-α-tocopherol) was used in these compositions, all showed an increase in oxidative impurities. This suggests that the initial concentration of the impurities has at least as much effect on the formation of additional oxidative impurities as does an excess concentration of d,l-α-tocopherol (i.e., outside the instantly claimed range).

b. The instantly claimed range of d,l-α-tocopherol is 0.001% to 0.5%. However, Rubino et al. teaches just three concentrations of d,l-α-tocopherol; 0.2%, 0.5% and 1%, which clearly do not encompass the full range instantly claimed.

c. Applicants have not provided a comparison of the instant claims with the closest prior art (e.g., Haeberlin et al.). Page 6 of Haeberlin et al. present comparative results of macrolide degradation in various compositions. The compositions comprise, *inter alia*, a surfactant, alcoholic solvents, malonic acid and d,l-α-tocopherol (0.1%, which is approximately the middle of the instantly claimed range). The disclosed comparative compositions vary by the presence or absence of malonic acid and the particular macrolide present.

Therefore, for the above reasons, especially items (a) and (b) and the lack of a showing commensurate in scope with the instant claims, Applicants have not demonstrated the criticality of the instantly claimed concentration range of d,l-α-tocopherol.

Finally, Applicants argue that the Examiner's assertion that the substitution of citric acid for malonic acid in a composition exemplified by Haeberlin et al. would have been obvious is incorrect. Applicants argue, "[i]n order to make this argument, the Examiner requires that one of skill in the art be led to remove the malonic acid of Haeberlin. Such motivation would be contrary to the teachings of Haeberlin. Not only do the formulations Haeberlin require an acid, but that the malonic acid component '...exhibits a pronounced stabilizing effect on the degradation of 40-O-(2-hydroxy)ethyl rapamycin and rapamycin' [last paragraph, at page 6 of Haeberlin]. Removing the acid component, particularly the preferred malonic acid component, from Haeberlin's formulations would be contrary to its teachings and destroy the advantages provided by the formulations described therein. Therefore, one of skill in the art would not be motivated to remove any acid from the formulation of Haeberlin and specifically the malonic acid as proposed by the Examiner."

The Examiner respectfully disagrees. The quotation of Haeberlin et al. to which Applicants are referring (i.e., last paragraph, at page 6 of Haeberlin) is in regard to the *exemplary* formulations disclosed on page 6. However, as discussed above, Haeberlin et al. teach the "[p]referred acids include malonic acid, oxalic acid, **citric acid**, and lactic

acid." (*see* page 4, lines 15-22). Thus, it is clear from Haeberlin et al. that one can substitute e.g., citric acid for malonic acid in the disclosed compositions.

Conclusion

8. Claims 13-16, 18, and 31-39 are rejected.

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1614

/James D Anderson/
Primary Examiner, Art Unit 1614